Industry perspective on the use of Post-Approval Change Management Protocol

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Agenda

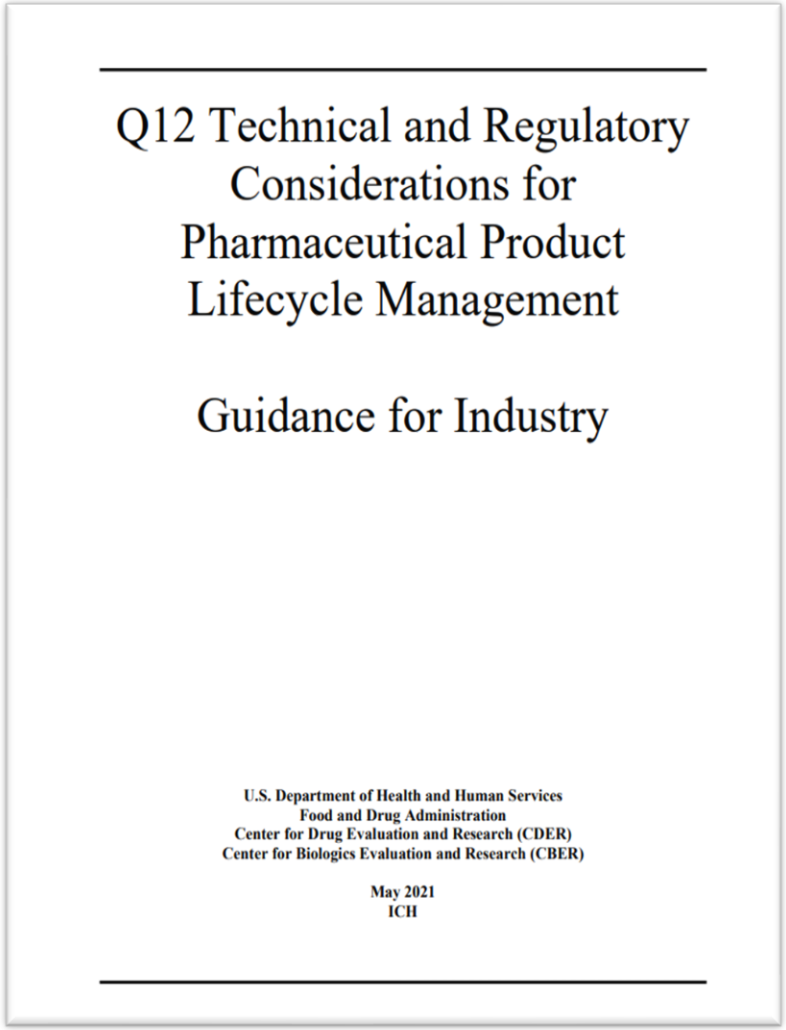
- *Introduction to Post Approval Change Management Protocols*
- *Types and applications of PACMPs*
- *Case sharing*
- *Reflections & Learnings*

What is a PACMP?

Post-Approval Change Management Protocol (PACMP)

Comparability Protocols

A protocol **describes the CMC change** an MAH intends to implement during the commercial phase of a product lifecycle, how the change would be **prepared and verified**, including **assessment of the impact** of the proposed change, and the **suggested reporting category** in line with regional regulations and guidance, i.e., a lower reporting category and/or shortened review period as compared to similar change procedure without an approved PACMP.



Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

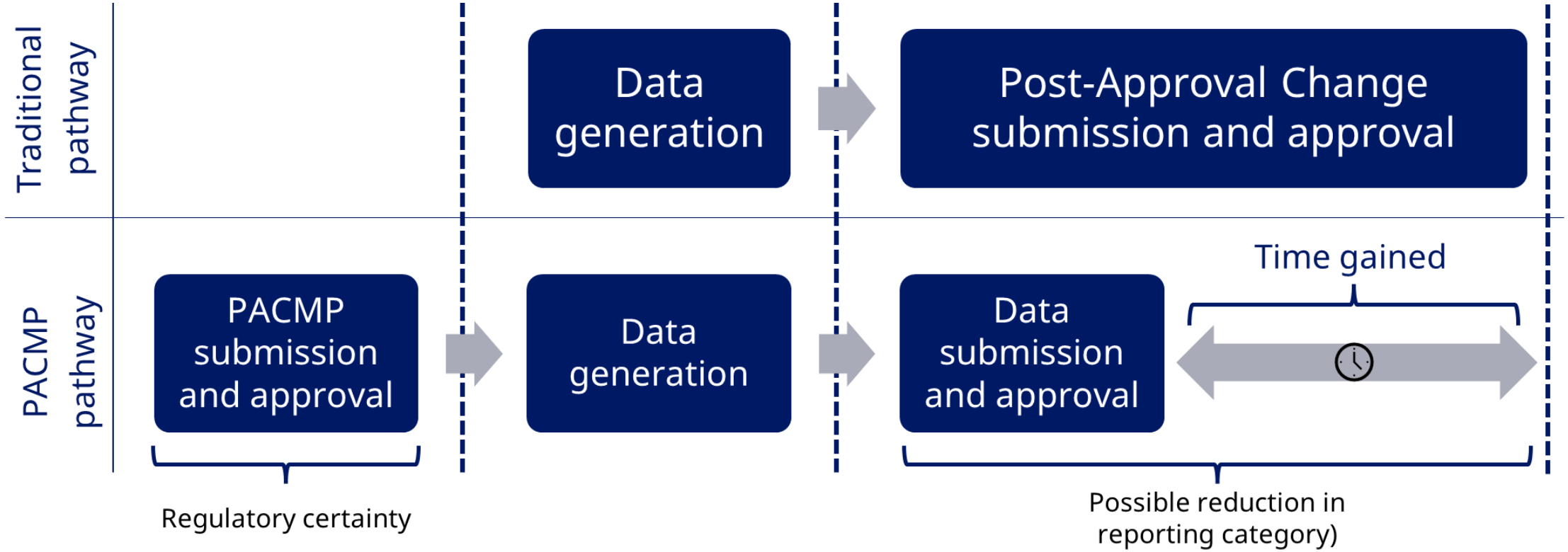
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2021
ICH

Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management Guidance for Industry. May-2021

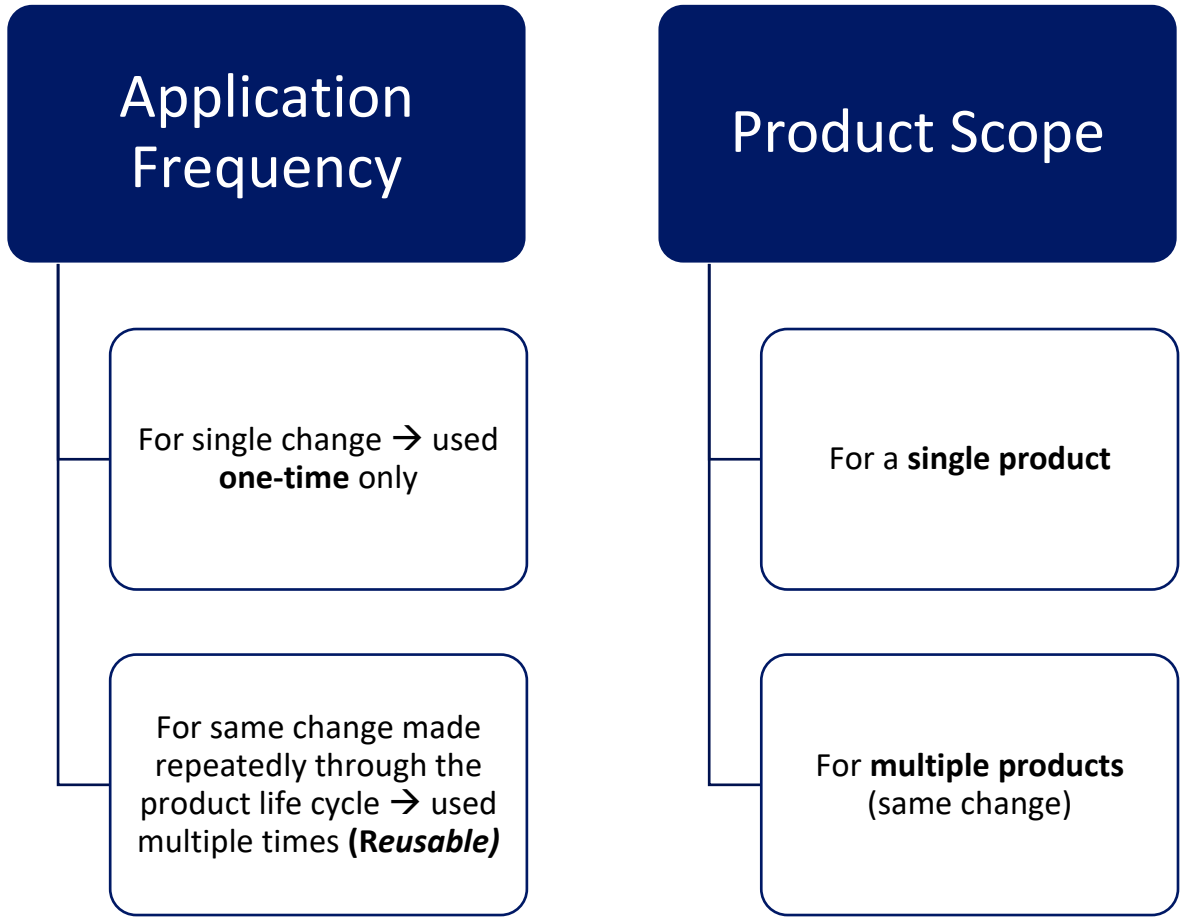
Two-step approach



Advantages gained from an approved PACMP

- Gain **prior agreements** on the supportive data required to support a submission of a proposed CMC change
- Possibility of a **lower reporting category** of the submission that would otherwise be a major change
  - Provides a major advantage as changes can be implemented earlier
  - Fast approval from EMA, FDA, Swissmedic enables faster submission of said change in other countries dependent on approvals from these authorities

Types and applications of PACMPs



EMA and FDA have guidance on reusable PACMPs

EMA: Questions and answers on post approval change management protocols. 30 March 2012. EMA/CHMP/CVMP/QWP/586330/2010. Committee for Medicinal Products for Human Use (CHMP)

8. Can a post approval change management protocol cover multiple changes?

It is possible to cover more than one change in a single protocol provided that they are directly related and a simultaneous review under a single protocol is meaningful. A justification should be provided in the protocol.

Depending upon the specific nature of the change(s), it is also possible for the content of a protocol to be applied on more than one occasion, e.g., new manufacturer of active substance starting material. However, this will depend upon successful implementation each time, in line with the protocol. In addition, the possibility will need to be transparent and therefore, if applicable, clearly stated in the protocol itself.

FDA: Comparability Protocols for Post-approval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA. Guidance for Industry. October 2022

6. What are FDA's recommendations regarding CPs for CMC changes that can be made repeatedly over the life cycle of a product?

A CP can be designed to be used repeatedly for a specific type of CMC change over the life cycle of a product. You should address the risk of adverse effects on product quality as a result of such cumulative changes over time in the supporting information for the CP. The CP should be designed in such a way to ensure that the effects of such cumulative changes will not result in an unintentional drift in product quality over time. Also, you should reevaluate the CP before each use to ensure that it remains scientifically sound. A notification using the reporting category specified in the approved CP must be submitted to the application each time a change is implemented according to the approved CP.[64] Each notification should include the data to demonstrate that all of the predefined acceptance criteria in the approved CP for successful implementation of the change were met.

Case Sharing

Case I : Changes in API purification process

- Change of RP-HPLC column to ultrafiltration/diafiltra units
- Revised process parameters
- No change to API specification

- **One-time** PACMP used

Analytical programme proposed in the protocol

- Drug substance Process Validation
- In-process control testing
- Drug substance release specification testing
- Comparative characterization (impurity profile)
- Accelerated stability study
- Additional tests for process-related impurities

Outcome and advantages gained

Authority	Usual classification	Classification after approved PACMP
FDA	PAS	CBE-30
EMA	Type II	Type IB (B.I.e.5.c)
Swissmedic	Type II	Type IB (B.I.e.5.c)

Prior-agreement → Regulatory certainty

Lower reporting category → Faster approval

Different questions received from different Authorities → revisions in individual PACMPs submitted → slightly diffferent PACMPs approved

Case II : Addition of drying equipment

- Same drying process as original equipment
- Overall design of the additional equipment comparable to the original
- Equipment introduced at the same API manufacturing site as original
- No change to in-process controls or API specification

➢ **Reusable** protocol submitted in EU, UK, CH and US

- The PACMPs submitted to each authority can be reused to implement the same change multiple times.

Analytical programme proposed in the protocol

- Drug substance Process Validation
- Drug substance release specification testing
- Comparative characterization (impurity profile)
- Accelerated stability study

Outcome and advantages gained

Authority	Usual classification	Classification after approved PACMP
FDA	CBE-30	CBE-30
EMA	Type IB by default (B.I.a.2.a)	Type IB (B.I.e.5.c)
Swissmedic	Type IB by default (B.I.a.2.a)	Type IB (B.I.e.5.c)

Prior-agreement → Regulatory certainty

No reduction reporting category was required

Different questions received from different Authorities → revisions in individual PACMPs submitted → slightly diffferent PACMPs approved

Case III: Addition of Drug Product Formulation & Filling (F&F) sites

- No changes to:
  - approved manufacturing process
  - in-process controls
  - drug product specification
  - approved container closure system
- Possible batch size upscale → to be justified as part of implementation

Proposed analytical programme:

- ✓ Process Validation*
- ✓ In-process control testing
- ✓ Release testing
- ✓ Stability testing

Outcome & Advantage → Prior agreement + Type-IB/CBE-30 reporting category

* *Process Validation not part of proposed testing programme for FDA if product is not a biologic. PV completed prior to release to market*

Submission strategy – F&F site addition

Different submission approach

Reusable PACMPs have been used

Intended to be used for multiple future sites

Only one-time CPs have been used

One-time CP submitted only to FDA (F&F site)

C. Facility Changes

Can a CP be used for a change in the location of an operation to a different facility?

Changes in the location of an operation to a different facility can be proposed in a CP, but because these changes will generally involve a facility evaluation, they generally do not justify a

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reporting category other than a PAS or CBE-30 supplement. Such facility evaluations may include factors such as the facility's prior inspection history, prior manufacturing experience with the dosage form that is the subject of the change, and the effectiveness of the facility's pharmaceutical quality system. This type of evaluation cannot be effectively conducted at the time of the CP submission, because certain factors at the time the change is to be implemented may be different from those at the time the CP is submitted. Based on this evaluation, FDA may determine that an inspection of the proposed facility is needed before making a decision on the supplement's approvability. In addition, for products that are difficult to characterize, site changes are more likely to need a preapproval inspection and therefore, in many cases, a reporting category lower than PAS would not be justified.

Comparability Protocols for Post-approval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA. Guidance for Industry. October 2022

Case example: Addition of a CMO (FDA)

- Established Contract Manufacturing Organization (CMO) but no prior experience with said pharmaceutical form
- No recent FDA inspection history

- FDA approved comparability protocol and a **potential** reporting category of CBE-30 with the following commitments:
  - A **Prior-Approval Supplement** will be submitted if the proposed facility is **not in compliance to 21 CFR Part 4** at the **time of supplement submission**
  - Agency may determine that a **CBE-30 category may not be justified** if updated **facility assessment or risk assessment** based on CMC information submitted **at the time of change implementation does not support it**

Additional information required by FDA at the time of CP submission (F&F site)

- **Description of facility**, classification of room, material/personnel movement etc.
- **Equipment** used in manufacture and sterilization
- **Sterilization methods** and validation of sterilization including acceptance criteria
  - *Validation results should be included with comparability report*
- **Environmental monitoring programme**
- Methods and procedures for **media fills** including acceptance criteria
  - *Validation results should be included with comparability report*

Reflections & Learnings

- PACMPs are a great tool to get prior agreements with authorities that ensure **predictability** and **regulatory certainty** for post-approval changes

- They are very useful for major changes for which **lower reporting category** is expected (and approved)
  - Major logistical advantage as time from manufacturing to release can be shortened

- Submission strategy, content of protocol, and the final protocol approved by different authorities may differ due to varying requirements and/or revisions during review

Thank You